REMARKS/ARGUMENTS

By this Amendment, claims 1, 3, 16, 88 and 89 are amended. Claims 1, 3, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82-101 are pending and under consideration.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2005/0085417 (Wickstrom et al.). Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the amendment to claims 1, 88, 89 for the limitation wherein the at least one (P) is covalently conjugated to at least one targeting moiety can be found in ¶[0047] and ¶[0064]; support for the amendment to claim 16 for the limitations "FE" and "Eu" can be found in ¶[0048]. No new matter is added by this amendment.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Withdrawn Rejections

Applicant gratefully acknowledges the withdrawn rejections.

Rejection under 35 U.S.C. 112, second paragraph

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner argues that in the first three lines claims 1, 88, and 89 recite that the therapeutic moiety is directly associated with the targeting moiety and with the PNA (i.e., P-X-T) and later the claim recites that the therapeutic moiety is indirectly associated with the targeting moiety via PNA (i.e., X-P-T). Since it is not clear what arrangement is claimed, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 90-101 are rejected for being dependent from the rejected claim 1 and also for failing to further clarify the basis of the rejection. For examination purposes, the claims are interpreted as being drawn to a compound with the formula X-P-T.

Without acquiescing to the propriety of the Examiner's rejection, and solely in an effort to expedite prosecution, the claims have been amended to recite that the compound comprises a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P),

which is covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. 112, first paragraph

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner argues that the amendments to the claim to include the term a therapeutic or diagnostic agent covalently conjugated to a targeting moiety (claims 1, 88, and 89) and "Fe(III), Eu(III)" introduce new matter. The Examiner further argues that while Applicants point to paragraph 0047 of the published application as supporting the amendment to claim 1, 88, and 89, and to paragraph 0065 as supporting the recitation of "Fe(III), Eu(III)". It is noted that the indicated paragraph 0047 recites a diagnostic moiety comprising a dendrimer conjugated to diagnostic compounds; there is no recitation of the diagnostic moiety being directly conjugated to a targeting moiety. The indicated paragraph 0065 discloses linkers and not diagnostic compounds. It is noted that paragraph 0048 does recite Fe and Eu however, there is no recitation of "Fe(III) or Eu(III)". Fe and Eu could also be divalent and the general recitation of Fe and Eu does not provide support for the specific selection of Fe(III) and Eu(III). A search of the remaining portions of the specification failed to provide literal support for such recitations.

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F .2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575,227 USPQ 177,179 (Fed. Cir. 1985)

(quoting In re Kaslow, 707 F.2d 1366, 1375,217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See M.P.E.P. § 2163.02. In this case, the skilled artisan would not have reasonably concluded at the time of the invention that applicant was in possession of the entire invention as claimed.

Here, in addition to the disclosures as cited in the previous response, the Specification discloses that (¶[0064]):

> The diagnostic or therapeutic moiety can be conjugated directly to a PNA, or can be conjugated to a PNA through one or more linking moieties. Multiple PNAs can be individually conjugated to different reactive groups on a diagnostic or therapeutic moiety. Alternatively, multiple PNAs can be conjugated to each other in series, and then conjugated to a single reactive group on a diagnostic or therapeutic moiety. Multiple PNAs conjugated to each other in series can optionally be separated from each other by one or more linking moieties.

Thus, the Specification clearly discloses a therapeutic or diagnostic agent covalently conjugated to a targeting moiety, since ¶[0047] discloses:

> In one embodiment, a diagnostic moiety of the invention comprises a compound conjugated to a single diagnostic center. In a preferred embodiment, a diagnostic moiety of the invention is formed by conjugating a polymer, preferably a dendrimer, with a plurality of diagnostic centers. As used herein, "conjugated" means that two chemical moieties are joined by a chemical bond or by a linking moiety. Examples of chemical bonds are covalent, hydrophilic, ionic, or hydrogen bonds. A preferred chemical bond is a covalent bond.

In addition, without acquiescing to the propriety of the Examiner's rejection, and solely in an effort to expedite prosecution, claim 16 has been amended to recite "Eu" and "Fe".

Clearly, the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., in view of both Basu et al. and Meade et al. This rejection is respectfully traversed.

The Examiner argues that Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer such as PMAM (i.e., polymeric diagnostic or therapeutic moiety, which is a branched oligomeric polychelant) or Starburst, M represents a carried material such as PNA, T represents a targeting moiety that can be an antibody fragment such as Fab, Fab', and wherein M and T are associated with the dendrimer via the same or different linkers (i.e., covalent bond), and that the linkers could be cleavable.

However, the claims are patentable over the combination of the Tomalia et al., in view of both Basu et al. and Meade et al. for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" ('166 Tomalia at column 47, lines 55-62). The other recitations of the (T)e*(P)x*(M)y structure ('166 Tomalia at column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point in the 5,714,166 patent do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples.

Therefore, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

While the Examiner admits that Tomalia et al. do not teach the specific arrangement X-L 1-P-L2-T recited in the instant claims, the Examiner argues that Tomalia et al. teach all components necessary for this arrangement. The Examiner argues that it is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The Examiner further argues that the arrangement is not significant if it does not provide a novel feature, and that it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. The Examiner sets forth that absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

However, in contrast to the instant claims, Tomalia et al. actually teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds, *. The instant claims, which are directed to a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not taught or suggested by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound. In addition, the claims are directed to spacers of from 10Å – 30Å, which is not taught or suggested in the Tomalia reference.

While the Examiner argues that although Tomalia et al. teach cleavable linkers, the Examiner admits that they do not specifically teach a biodegradation cleavage site, but argues that Meade et al. teach a biodegradation cleavage site. The Examiner argues that it would have

been obvious to one of skill in the art, at the time the invention was made, to include a biodegradation cleavage site, as taught by Meade et al., with a reasonable expectation of success. The Examiner argues that the motivation to do so is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target.

The Examiner disagrees with Applicant's argument that at no point do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer. The Examiner argues that Tomalia et al. teach a compound with the formula (T)e*(P)x*(M)y wherein M represents a diagnostic or therapeutic agent, T represents a targeting moiety, and P represents a dendrimer; M could be associated with the dendrimer via a covalent bond and M could be a nucleic acid such as PNA. The Examiner concludes that Tomalia et al. do not teach away from covalent bonding of genetic materials to dendrimers and concludes that Basu or Meade references have nothing to remedy.

However, if as the Examiner argues, Basu and Meade do not have anything to remedy, it is unclear why they were cited. In any event, the deficiencies in the Tomalia reverences are not cured by the Basu or Meade references. Basu et al. reported a construct of the form P-L2-T designed to bind to a specific cellular receptor, internalize to the cytoplasm, and bind to its specific target mRNA. The construct as disclosed in the Basu reference does not contain a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, and does not contain a spacer L1. One skilled in the art would therefore not have been motivated by Basu, et al. to covalently bond X-L1 to P-L2-T. Additionally, as noted above, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

The secondary references Meade and Basu do not remedy the aforementioned deficiency of the primary reference, the Tomalia et al. patent, to teach or suggest all the limitations of the claims because Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Meade only taught that water access to a Gd(III) reporter for MRI could be achieved by biodegradation of a protecting peptide strip over the top of a chelator binding the Gd(III). Moreover, it would not be obvious to a person skilled in the art to modify the teachings of Tomalia with Meade and Basu to reach all the limitations of the claims, for the reasons set forth in the Declaration of Dr. Eric Wickstrom.

Applicant has previously submitted a Declaration under 37 CFR § 1.132 of Dr. Eric Wickstrom, submitted December 19, 2007. Here, the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu patents to teach or suggest the claimed invention.

However, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. See In re Ratti, 270 F.2d 810 (CCPA 1959). This is shown here.

However, as shown in the Declaration, Applicants' attempt to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the In re Ratti case, therefore the claims are patentable.

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicants attempted to use the Tomalia teachings as the basis for reaching the claimed invention, but were unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

The Examiner further argues that Tomalia et al. do teach that the linkers are used to avoid steric hindrance (column 17, lines 40-60). The Examiner argues that the purpose of Tomalia et al. is obtaining a composition suitable for targeted delivery. The Examiner sets forth that the argument that Applicant was unsuccessful to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia is not found persuasive, allegedly because the prior art teaches how to successfully link dendrimers to nucleic acids nucleic acids via a covalent bond.

The Examiner cites Goh et al. which allegedly teaches solid-phase synthesis of covalent dendrimer-oligonucleotide conjugates by linking dendrimers to oligonucleotides attached to solid supports (p. 2954 and 2955). Additionally, Basu et al. teach solid phase synthesis of targeting ligand-PNA conjugates, wherein the targeting ligand is automatically synthesized on a solid support, followed by the assembly of the PNA. The Examiner concludes that by reading Basu et al. and Goh et al., one of skill in the art would know how to successfully extend a dendrimer from a solid phase-attached ligand-PNA.

However, Goh, et al. teach extension of ester-linked dendrimers from the termini of normal DNA oligonucleotides. But blood and cells contain significant concentrations of nucleases and esterases. Those skilled in the art are aware that normal DNA is rapidly degraded in blood and cells by nucleases. Thus, designers of DNA analogs for administration to animals and humans are aware of the need to create derivatives that resist nucleases.

Similarly, those skilled in the art are aware that ester linkages are rapidly degraded in blood and cells by nonspecific esterases. Thus, designers of dendrimers for administration to animals and humans are aware of the need to create derivatives that resist esterases.

As a result, Goh et al. teach away from the composition of matter in the instant application, which depends on DNA analogs with amide linkages that are resistant to nucleases, and dendrimers with amide linkages that are resistant to esterases. Therefore, one of skill in the art would not consider application of the methods of Goh, et al. to prepare agents for imaging or therapy in animals or humans.

The Examiner further argues that the Declaration does not provide any evidence that this is not possible and moreover, the specification teaches that one of skill in the art would easily link a dendrimer to a ligand-PNA.

However, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicants demonstrate that attempting to use the Tomalia teachings as the basis for reaching the claimed invention were unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the

PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

SBIR

In addition, Applicant has recently had a Small Business Innovation Research (SBIR) grant, (Pak, Koon Y, SBIR Phase I FT R44CA136306-01, Radiohybridization Imaging of HER2 Oncogene to Detect Breast Cancer, 2008, copy attached, and cited on the IDS submitted herewith), funded by the United States National Institutes of Health. The Small Business Innovation Research (SBIR) program is a program for domestic small business concerns to engage in Research/Research and Development (R/R&D) that has the potential for commercialization.

Applicant has designed and demonstrated a novel technology to see visualize hyperactive cancer genes from outside the body, which is called radiohybridization imaging (RHI). RHI scans the entire organ or body to find all sites of cancer gene activation, whether or not a lump has formed. RHI probes are peptide nucleic acid (PNA) sequences that hybridize specifically to messenger RNAs (mRNAs) copied from activated cancer genes. Applicant added a small peptide analog to allow the RHI probes to be taken up by breast cancer cells. Finally, they chelated radionuclides to permit external imaging by positron emission tomography (PET) scanning. RHI probes for CCND1, IRS1, MYCC, and KRAS mRNAs, injected into animal models, enabled the visualization of breast cancer, pancreas cancer, and prostate cancer xenografts. High levels of human epidermal growth factor receptor 2 (Her2) protein are associated with aggressive, invasive, estrogen-independent breast cancers.

In the Grant Application, Applicant has demonstrated that [99mTc]peptide-PNA probes do not provide tumor images without an IGF1 analog, or without a complementary PNA. However, specific imaging of MYCC mRNA expression in MCF7:IGF1R breast cancer xenografts was observed with a specific [99mTc]peptide-MYCC PNAIGF1 analog. The probes are not rapidly metabolized into fragments. These results demonstrate imaging of oncogene expression in vivo with [99mTc]chelator-PNA-IGF1 analogs (see Figures 4- 6).

Applicant has demonstrated that CCND1 cancer gene activity in ER+ xenografts can be detected specifically from outside the body by probing with [99mTc]chelator-PNA-IGF1 analog chimeras (see Figures 7-12).

Applicant has demonstrated the preparation of PET probes for CCND1 mRNA, and image those mRNAs in human BT474 Her2+ breast cancer xenografts in immunocompromised mice. This is a stringent test, because CCND1 mRNAs are not expressed as strongly in Her2+ breast cancer xenografts as they are in Her2- breast cancer xenografts, like the MCF7 xenografts they have already imaged successfully. These PET imaging results represent a rational basis for malignancy classification targeted to CCND1 mRNA, depending on their expression levels revealed by imaging (see Figures 13-17).

Applicant has demonstrated that CCND1 PET radiohybridization probes can identify sites of CCND1 overexpression in sporadic breast lesions, as opposed to normal mammary tissue (see Figure 18). This system is the closest possible model for the clinical situation. Furthermore, NIH has demonstrated confidence that the Applicant and industrial partners can accomplish a similar goal for HER2 overexpression and develop a clinically useful radiodiagnostic.

Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, and Basu references. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1, 3,4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73,75, 80, 82, 83, 86, and 88-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. This rejection is respectfully traversed.

The Examiner admits that Tomalia et al., Meade et al., and Basu et al. do not teach an oncogene, wherein the oncogene is K-RAS, nor do they specifically teach treating pancreatic cancer, but argues that Nakano et al. teach gene therapy by using antisense K-RAS as a therapeutic agent for cancer. The Examiner argues that it would have been obvious to one of skill in the art, at the time the invention was made, to use the compound and the method of Tomalia et al., Meade et al., and Basu et al., wherein the PNA is directed against K-RAS, to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express K-RAS, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-RAS transcript inside these cells. The Examiner argues that the rejection is maintained because Tomalia et al, Meade

et al, and Basu et al. do teach the claimed invention.

However, the Tomalia, Meade and Basu references were addressed above, and the addition of the Nakano et al. reference does not cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising therapeutic or diagnostic moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, and 89-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al., in view of Basu et al. This rejection is respectfully traversed.

The Examiner argues that Lewis et al. teach a DOTA-PNA conjugate designed to target bcl-2 (i.e., an oncogene), wherein DOTA comprises a radiometal and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linker.

The Examiner admits that Lewis et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, the Examiner argues that Lewis et al. teach all components necessary for this arrangement. The Examiner alleges that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. The Examiner argues that absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine

experimentation. The Examiner argues that one of skill in the art would know that the DOTA of Lewis et al. could substitute for polyethyleneimine, since both are known in the art to be efficient at delivery of nucleic acids to the cells.

However, DOTA is not comparable to polyethyleneimine in any aspect. The Examiner's statement to the contrary is a serious error. DOTA is a small, negatively charged cyclic molecule designed to bind positively charged metal ions. DOTA has no ability to facilitate DNA uptake into any cell. Polyethyleneimine is a large positively charged detergent polymer that is designed to bind negatively charged polymers, like DNA, for the purpose of creating a neutral particle capable of facile cell penetration.

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a chelator for radiometal cations (i.e., a non-polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, and is further coupled to a detergent-like PTD-4 peptide that facilitates intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety) into any cell. The detergent-like PTD-4 peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). The Examiner improperly equates a peptide detergent intended for universal intracellular delivery of the radiolabeled PNA (i.e., a membrane permeating peptide PTD-4) with a specific cell surface receptor targeting moiety of the present invention, which is defined in the specification on page 21, lines 20-21 as "a moiety that comprises any chemical substance that is capable of binding to a cell surface molecule or being bound by a cell surface molecule (e.g., a receptor)." In the instant claims, targeting the conjugate of the invention to a cell surface receptor so that the internalization is achieved via a receptor provides the desired specificity. This specificity cannot be achieved when a general membrane permeating peptide is used instead of a particular cell surface receptor ligand. Therefore, the membrane permeating peptide PTD-4 in Lewis et al. does not constitute a "targeting moiety" as contemplated in this invention.

The Examiner admits that Lewis et al. do not teach a targeting moiety capable of binding to a cell surface molecule, but argues that Basu et al. teach enhancing PNA delivery to cells by receptor-mediated endocytosis via coupling the PNA to ligands for cell surface receptors.

The Examiner argues that with respect to the limitation of pharmaceutical composition, the transfection buffer comprising the conjugate is a pharmaceutical composition. With respect

to the specific linkers and their length, absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA, these are inherent to a method using PNA.

The Examiner argues that it is noted that the instant rejection is an obviousness-type rejection and therefore, Lewis et al. do not have to teach each and every claim limitation. It is the combination of Lewis et al. and Basu et al. which teaches a composition comprising a ligand for a cell surface receptor. The Examiner further argues that with respect to the linkers, beside an argument, Applicant did not provide any evidence that he was the first to introduce these linkers introduced into PNA constructs. It is noted that the use of linkers to inhibit steric hindrance between in PNA construct is taught by the prior art (see the teachings of Tomalia et al. above). The Examiner argues that optimizing the linker type and their size only requires routine experimentation

However, the Examiner erroneously equates a short bifunctional linker, *, intended only to connect the components of (T)e*(P)x*(M)y, with the instantly claimed flexible, hydrophilic spacer, L, 10-30 Å long, in X-L1-P-L2-T, intended to prevent functional interference between the PNA, P, and the moieties, X and T, attached to either end. Such spacers have only been introduced into such PNA constructs by the Applicants, as shown in their published papers. Any other use of such spacers to separate PNA from peptides or reporters appeared later, in imitation of Applicant's published strategy. Accordingly, the combination of the references does not teach or suggest all the claim limitations as asserted by the Examiner.

In addition, the claims are directed to a compound comprising a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, wherein the PNA comprises a base sequence that is complementary to a target nucleic acid sequence, or pharmaceutically acceptable salts thereof. While the Basu reference discloses an IGF1 moiety, there is no teaching or suggestion of a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T)

that selectively binds to a cell surface receptor, nor is a therapeutic or diagnostic moiety taught or suggested in the Meade reference.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of Nakano et al.

The Examiner argues that the teachings of Lewis et al. and Basu et al. are applied as above, and alleges that Nakano et al. teach gene transfer antisense K-RAS as a therapeutic agent for cancer. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al. and Basu et al. by using a PNA directed against K-RAS and use it in a method of delivering diagnostic and therapeutic agents to cancer cells over-expressing K-RAS, such as colon and pancreatic cancer cells, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-RAS transcript inside these cells.

However, the Lewis, and Basu references were addressed above, and the addition of the Nakano et al. reference does not cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising targeting moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1,3,4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, and 88-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in further view of both Tomalia et al. and Meade et al.

The Examiner argues that the teachings of Lewis et al. and Basu et al. are applied as above, and that the teachings of Tomalia et al. and Meade et al. are applied as above. Lewis et al. and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration. Tomalia et al. and Meade et al. teach these limitations. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al. and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success. One of skill in the art would have been motivated to use the dendrimers of Tomalia et al. because the art teaches dendrimers as being very efficient in delivering agents to cells.

However, as discussed above, the Lewis, Liang and Basu references do not teach or suggest a conjugate comprising "a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor", and this deficiency is not cured by the Tomalia or Meade patents, because, as set forth above, as evidenced by the Declaration of Dr. Eric Wickstrom, attempting to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, and Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, Tomalia, and Meade references.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
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July 27, 2009

By _____

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.